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10/585,651	07/07/2006	Philip C. Trackman	BU-112XX	5481

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EXAMINER	
MEAH, MOHAMMAD Y	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/585,651	TRACKMAN ET AL.	
	Examiner	Art Unit	
	MD. YOUNUS MEAH	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/7/09*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *8-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-15 are currently pending in the instant application. Claim 8-15 remain withdrawn.

Applicants' arguments filed on 4/7/09, in response to a previous office action mailed on 1/7/2009, have been fully considered but they are found unpersuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. In the prior office action of 1/7/09 Examiner inadvertently omitted to indicate that the election of species requirement made in the restriction requirement of office action of 09/10/2008 has been withdrawn.

Sequence compliance

As previously indicated, Applicant is required to comply with the sequence rules by inserting the sequence identification numbers of all sequences recited within the claims and/or specification. For example see the specification at page 22 lines 20 and 21. Appropriate correction is required. See particularly 37 CFR 1.821(d). Applicants in their response of 4/7/09 stated that a corrected sequence listing will be submitted shortly. However, since it has not been submitted yet, the previous objection is maintained for the reasons of record.

Objection

Figures 3A-3D remain objected because they contain amino acid sequences designated by lower case letters. It is the convention in the art to write amino acid sequences that use one letter symbols with upper case letters. Appropriate correction is required. Applicants in their response of 4/7/09 stated that they will submit the

appropriate replacement Figures shortly. However, since they have not been submitted yet, the previous objection is maintained for the reasons of record.

Claim 1, is objected in reciting "portion of lysyl oxidase..". It should be replaced by "portion of a lysyl...". Appropriate correction is required.

Claim 4, is objected in reciting "sequence given in SEQ .." It should be replaced by "sequence of SEQ ..." Appropriate correction is required.

Claims 4, 5, are objected in reciting "..portion of the amino acid sequence.." It should be replaced by "...portion of the polypeptide having the amino acid sequence..." Appropriate correction is required.

Claim 5, is objected in reciting "group consisting of SEQ ID NOs 3-8..." It should be replaced by "group consisting of SEQ ID NO:3, 4, 5, 6, 7 and 8". Appropriate correction is required.

Claim 6 a), is objected in reciting "inhibited by lysyl oxidase..." It should be replaced by "inhibited by the lysyl..." Appropriate correction is required.

Claim 6 is objected in reciting "identifying the active portion of lysyl.." It should be replaced by "identifying the active portion of a lysyl..." Appropriate correction is required.

claim 6 b), is objected in reciting. "fragment of lysyl..." It should be replaced by "fragment of the lysyl..." Appropriate correction is required.

Claim Rejection 35 U.S.C 112 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 4-5 (dependent on claim 1) remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite in recitation the phrase "a therapeutically active portion" because it is unclear what a therapeutically active portion constitute and what is the therapeutically activity. If the "activity" is inhibition of cell growth, it is suggested the term be amended accordingly

Claims 4, 5 and 6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite in recitation the phrase "active portion of " because it is unclear as to what activity is being referred to. A polypeptide can have any number of activities such as enzymatic activity, binding activity, elicitation of antibodies, etc. Since the "activity" is undefined, one cannot determine which portion of a polypeptide is required by the claims. If the "activity" is inhibition of cell growth, it is suggested the term be amended accordingly.

Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation of "d) .....with a smaller portion of said lysyl oxidase pro peptide, of length l_2" for the following reasons. It is unclear if the term is intended to refer to a portion of L_1 (i.e., fragment of the L_1 fragment), or if the term is intended to refer to a fragment of any size of the entire lysyl oxidase pro-peptide, wherein said fragment is L_2. For

examination purposes, the claim will be interpreted as "d)....with a smaller portion of the L_1 fragment, wherein said smaller portion has a length L_2..". Correction is required.

Applicant's arguments at page 7 of their amendment of 4/7/09 have been considered but found unpersuasive. Applicant argue that at pages 2-5, the specification describes lysyl pro-peptide shows tumor inhibiting activity, the tumor suppression activity of lysyl oxidase gene, whereas not showing lysyl oxidase activity. However claims refer to any therapeutic activity. Since the therapeutic activity is undefined in the claims, one cannot determine which portion of a polypeptide is required by the claims.

Claim Rejection 35 U.S.C 112, 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention as explained in prior office action and stated again bellow:

Claims 1-5 are directed to a therapeutic composition comprising the active portion of any lysyl oxidase pro-peptide lacking enzymatic activity from any source

having any structure (claims 1-3) or any lysyl oxidase pro-peptide variant (claims 4-5) wherein said variant comprises an amino acid sequence which results from any number of conservative substitutions in any one of SEQ ID NO: 1-8. The specification teaches the structure of only a few representative species of such lysyl oxidase pro-peptides and fragments thereof lacking enzymatic activity, i.e., the human polypeptides of SEQ ID NOs: 1, 3 and 6; the mouse polypeptides of SEQ ID NOs: 2, 4 and 7, and the rat peptides of SEQ ID NOs: 5 and 8. The SEQ ID NOs: 1 and 2 are full length lysyl oxidase pro-peptides and SEQ ID NO: 3-8 are fragments of human, rat and mouse lysyl oxidase pro-peptides comprising 35-38 amino acids. The specification fails to describe any other representative species by any identifying characteristics or properties other than the biological activity lacking enzymatic activity. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

In University of California v. Eli Lilly & Co., 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice,

reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

In the instant case the scope of the instant claims encompass a genus of polypeptides which are lysyl oxidase pro-peptides lacking enzymatic activity from any source or any variant comprising an amino acid sequence that results from making any number of conservative substitutions in SEQ ID NOs: 1-8 , wherein said variants can have any activity. Thus, the claimed therapeutic composition comprises a polypeptide **having any structure**. The prior art, as evidenced by WO/0185157, teaches a few lysyl oxidases and the specification teaches (page 3) three lysyl oxidase pro-peptides and fragments thereof(SEQ ID NOs: 1-8). However, the specification fails to describe any other representative species by sufficient identifying characteristics or properties to show that applicant was in possession of the claimed genus.

There is no structure-function correlation with regard to the members of the genus of polypeptides required in the claimed therapeutic compositions While the specification discloses that the pro-peptide of a lysyl oxidase can be used in treating

forms of cancer that are dependent upon ras signaling for cell transformation, the specification is silent with regard to the biological activity of any variant of any pro-peptide as recited, or whether any variant as recited would have the same cell proliferation inhibiting activity found with the pro-peptide tested. Therefore one of skill in the art would not recognize from the disclosure that applicants' were in possession of the claimed inventions. Applicants' are referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Applicants arguments against rejection of claims 1-5 under 35 U.S.C. 112, first paragraph written description are acknowledged but are not found persuasive because as explained in the prior rejection and above, knowledge of the structure of the lysyl oxidase is essential to find out which portion of the pro-peptide is therapeutically active, without such knowledge it is not possible to find out the recited active portion. Furthermore, while the claims encompass structural variants of any lysyl oxidase pro-peptide, the specification and the art are completely silent with regard to the structural features required in any of these variants such that they can have cell growth inhibiting activity. There is no structure/function correlation which would allow one of skill in the art to determine the structural variations that can be made to any lysyl oxidase pro-peptide and observe cell growth inhibition. Therefore the specification fails to sufficiently describe the claimed invention.

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for therapeutic composition comprising any of the peptides of SEQ ID NOs:1-8, and a method of identifying the minimum portion of the lysyl oxidase pro-peptides of SEQ ID NO: 1 or 2 which has cell growth inhibiting activity, , does not reasonably provide enablement for (A) any therapeutic composition comprising (1) any lysyl oxidase pro-peptide or fragments thereof, (2) any structural variant of the polypeptides of SEQ ID NO: 1-8 having any activity, wherein said variant is the result of any number of conservative substitutions, or (B) a method of identifying the smallest fragment of any lysyl oxidase pro-peptide which has cell growth inhibiting activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

According to MPEP 2164.01(a), factors considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

MPEP§ 2164.04 states that while the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the

evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection. The language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims. Accordingly, the factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: Claims 1-7 are broadly directed to include (A) any therapeutic composition comprising (1) any lysyl oxidase pro-peptide or fragments thereof, or (2) any structural variant of the polypeptides of SEQ ID NO: 1-8 having any activity, wherein said variant is the result of any number of conservative substitutions, and (B) a method of identifying the smallest fragment of any lysyl oxidase pro-peptide which has cell growth inhibiting activity. The enablement provided is not commensurate in scope with the claim due to extremely large number of proteins encompassed by the claims for which their structure and/or function are unknown. In the instant case, the specification enables a therapeutic composition comprising any of the peptides of SEQ ID NOs:1-8, and a method of identifying the minimum portion of the lysyl oxidase pro-peptides of SEQ ID NO: 1 or 2 which has cell growth inhibiting activity

The state of the prior art; The relative skill of those in the art; and The predictability or unpredictability of the art:

Methods for isolating proteins or generating variants and mutants using random mutagenesis techniques were known in the art. However, neither the specification nor the state of the art at the time of the invention provided the necessary guidance for (1) correctly identifying based solely on structural features which proteins from any source have lysyl oxidase activity so that their pro-peptide can be identified, or (2) altering the amino acid sequence of any lysyl oxidase pro-peptide to obtain a peptide which would have cell growth inhibiting activity. There is no guidance as to which positions within SEQ ID NO: 1-8 can be tolerant of conservative substitutions and which amino acids can be used as substitutes so that the recited variants can also inhibit cell growth. At the time of the invention, there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the same desired biological activity.

The amino acid sequence of a protein determines the structural and functional properties of that protein. In the instant case, neither the specification nor the art provide a correlation between structure and cell growth inhibiting activity such that one of skill in the art can envision the structure of any of the peptides recited in the claims having the desired biological activity. Predictability of which changes can be tolerated in a protein's amino acid sequence to obtain a desired biological activity, requires knowledge and guidance regarding which specific amino acid residue(s) in the protein's amino acid sequence, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification) and detailed knowledge of the protein's structure, and the ways in which the protein's structure relates to its function. In addition, one skilled in the

art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g., multiple substitutions, deletions, additions, and combinations thereof. The reference of Chica et al. (Curr Opin Biotechnol. 2005 Aug; 16(4):378-84) teaches that the complexity of the structure/function relationship in enzymes has proven to be the factor limiting the general application of rational enzyme modification and design, where rational enzyme modification and design requires in-depth understanding of structure/function relationships.

The amount of direction provided by the inventor; and the existence of working examples: While the claims are directed to compositions and methods that require any lysyl oxidase pro-peptide, or structural variants of the polypeptides of SEQ ID NO: 1-8 having any function, the specification fails to provide any specific guidance for obtaining any lysyl oxidase or its corresponding pro-peptide, nor does it provide any guidance as to which conservative modifications can be made to any of the peptides of SEQ ID NO: 1-8 such that they would display cell growth inhibiting activity.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of isolating and/or generating variants of a polypeptide were known in the art at the time of the invention and the specification provides general teachings for searching and screening for the claimed invention, it was not routine in the art to screen by a trial and error process for all polypeptides having lysyl oxidase activity and their corresponding pro-peptides, nor was it routine in the art to make an infinite number of structural variants and test them for a desired activity.

The total number of variants of a polypeptide having a specific number of substitutions can be calculated from the formula N!x19^{A}/(N-A)!/A!, where N is the length in amino acids of the reference polypeptide and A is the number of desired substitutions. Thus, for example, for a variant of the polypeptide of SEQ ID NO: 3 where 34 positions can be substituted with any of the remaining 19 amino acids, the total number of variants to be tested is 35!x19^{34}/(35-34)!/34! (SEQ ID NO: 3 has 35 amino acids) or 1.05x10^{45} variants. Even if it is assumed that each of the 34 positions can be replaced with an average of 3 amino acids (conservative substitutions), the number of variants amounts to 35!x3^{34}/(35-34)!/34! or 5.83x10^{17} variants. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, as is the case herein, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed so that a reasonable number of species can be selected for testing. In view of the fact that such guidance has not been provided in the instant specification, it would require undue experimentation to enable the full scope of the claims.

Therefore, in view of the specification's lack of specific guidance and additional working examples, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required, it would require undue experimentation for a skilled artisan to make and use the entire scope of the claimed invention. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of

enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988).

Applicants arguments against the rejection of claims 1-7 under 35 U.S.C. 112, first paragraph enablement requirement are not found persuasive Identification of any lysyl oxidase pro-polypeptide will require knowledge of the structure of such lysyl oxidase. The claims require any lysyl oxidase pro-peptide from any source. However, neither the specification nor the art provide any guidance as to the structures of all the lysyl oxidase pro-peptides required nor do they provide any teaching or suggestion as to how the ones disclosed in the specification and/or the prior art correlate with any lysyl oxidase pro-peptide.. Applicants argue that one of skill in the art can use conservative substitutions to find out the active portion of a lysyl oxidase pro-peptide. This is not found to be persuasive because without any knowledge of how the structure of any lysyl oxidase pro-peptide correlates with the ability to inhibit cell growth, the effect of making any number of conservative substitutions is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Claim Rejection - 35 U.S.C 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 remain rejected under 35 U.S.C. 102(b) as being anticipated by Li et al. (WO/0185157, November 15, 2001). Li et al teach a therapeutic composition comprising a lysyl oxidase polypeptide without catalytic activity for the treatment of cancer/tumors (page 10 lines 25-33, and page 13, lines 25-28).

Applicants' arguments presented at pages 9-10 of the response filed on 4/7/2009 traversing the instant 35 U.S.C. 102(b) rejection have been considered but not found to be persuasive because Li et al teach a lysyl oxidase which may not have catalytic activity but is therapeutically active. The lysyl oxidase of Li et al. having no catalytic activity would include the pro form of the enzyme (pro-peptide linked to the mature enzyme). Since claims 1-3 are directed to a composition that has a polypeptide that comprises the pro-peptide, the pro form of the lysyl oxidase of Li et al. having no catalytic activity is a species of the genus of polypeptides comprising the pro-peptide recited in claims 1-3. Limitations regarding inhibition of cell growth in agar or in inhibition of tumor formation are inherent to the pro form of the lysyl oxidase of Li et al. as evidenced by the specification which teaches that the lysyl oxidase pro-peptide has those activities. As such, the teachings of Li et al. anticipate the instant claims as written.

Allowable Subject Matter/Conclusion

Claims 1-7 are rejected and none of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mohammad Meah whose telephone number is 571-272-1261. The examiner can normally be reached on 8:30-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mohammad Younus Meah
Examiner, Art Unit 1652

/Delia M. Ramirez/

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